A generalized theory for current-source density analysis in brain tissue

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The current-source density (CSD) analysis is a widely used method in brain electrophysiology, but this method rests on a series of assumptions, namely that the surrounding extracellular medium is resistive and uniform, and in some versions of the theory, that the current sources are exclusively made by dipoles. Because of these assumptions, this standard model does not correctly describe the contributions of monopolar sources or of non-resistive aspects of the extracellular medium. We propose here a general framework to model electric fields and potentials resulting from current source densities, without relying on the above assumptions. We develop a mean-field formalism which is a generalization of the standard model, and which can directly incorporate non-resistive (non-ohmic) properties of the extracellular medium, such as ionic diffusion effects. This formalism recovers the classic results of the standard model such as the CSD analysis, but in addition, we provide expressions to generalize the CSD approach to situations with non-resistive media and arbitrarily complex multipolar configurations of current sources. We found that the power spectrum of the signal contains the signature of the nature of current sources and extracellular medium, which provides a direct way to estimate those properties from experimental data, and in particular, estimate the possible contribution of electric monopoles.

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I. INTRODUCTION

The current-source density (CSD) analysis [1, 3] is a method consisting of estimating the underlying current sources from a series of recordings of the extracellular electric potential. This method is widely used in neuroscience, and applies well to layered structures of the brain, such as cerebral cortex, hippocampus or cerebellum [1]. The CSD analysis is based on the "standard" model of electric potentials in biological tissue [1, 3, 4], which rests on the hypothesis that the extracellular medium is resistive (ohmic) and uniform. Other influences, such as ionic diffusion, are assumed to play a negligible role on the propagation of the electric field.

Based on this set of hypotheses, the equation that determines the electric potential at macroscopic scales ($\sim 50\ \mu m$ or more) is given by:

$$\nabla \cdot (\sigma^e \nabla V) = \sigma^e \nabla^2 V = \frac{\partial \rho}{\partial t}\,, \tag{1}$$

where σ^e is the electric conductivity of the extracellular medium. This expression can be obtained by applying the differential law of charge conservation and Ohm's law. The term $-\frac{\partial \rho}{\partial t}$ is interpreted as the volumic density I_m of current sources. This equation forms the basis of the CSD analysis method [1–3, 5].

According to Eq 1, the electric potential V would only depend on electric conductivity and not at all on electric permittivity. However, Poisson's law in a homogeneous medium ($\varepsilon \nabla^2 V = -\rho$) implies that V will be twice smaller for twice larger ε with the same charge distribution, so it is paradoxical that permittivity is not taken into account in CSD analysis. Moreover, according to Eq 1, the electric potential is determined solely by the charge conservation law, and independently of Poisson's law, which is contradictory with Gauss' law in Maxwell equations.

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If we take Gauss' law into account, we can write

$$\frac{\partial \rho}{\partial t} = \sigma^e \nabla^2 V = -\frac{\sigma^e}{\varepsilon}\rho,$$

The general expression for ρ is:

$$\rho(\vec{x}, t) = \rho(\vec{x}, 0) e^{-\frac{t}{\tau_{MW}}}$$

where $\tau_{MW} = \frac{\varepsilon}{\sigma^e}$ is the Maxwell-Wagner time of the medium. However, τ_{MW} is usually considered as negligible (typical values for biological tissue are $\tau_{MW} \approx 10^{-10}$ s, with $\sigma = 0.3$ S/m and $\varepsilon \approx 10^{-10}$ F/m) such that the current source density must be approximately zero, which is paradoxical. One way to resolve this paradox is to consider that the Maxwell-Wagner time is not negligible, or that electric parameters display strong spatial variations. However, such conditions contradict the hypothesis that the medium is resistive, and lay outside the domain of validity of Eq. 1 because in this case the impedance of the extracellular medium is complex in Fourier space [6, 7].

Despite this paradox, the standard model seems to apply relatively well to media such as brain tissue [1, 3]. This model has, however, the drawback that it cannot be used to determine the validity of the hypotheses it is based on. Moreover, there is no clear definition of microscopic or macroscopic levels, and consequently, it is difficult to include possible frequency dependencies that could result from different physical phenomena at intermediate (mesoscopic) scales, such as ionic diffusion or membrane polarization [7].

In the present paper, we introduce a more general formalism which does not rest on the hypotheses of classic CSD where the medium is hypothesized to be uniform and resistive, which also supposes that the electric parameters are constant and independent of frequency. The goal of this new formalism is to provide generalized expressions for CSD analysis in non-resistive media. Our aim is also to provide a theory which is general enough to enable testing different hypotheses concerning the nature of current sources and the electrical properties of the surrounding extracellular medium, which could then be directly estimated from experimental data.

II. GENERAL THEORY

In this section, we derive a mean-field theory of the electric field and potential resulting from current densities in biological tissue, by staying as general as possible.

A. Definitions and scales

In the generalized formalism presented below, we will define the current sources from conductance variations. We will assume that the differential law of charge conservation holds in a given domain D, without defining a current source density per unit volume. We assume that the conductance variations in cellular membranes (especially around synapses), within domain D, are the principal origin of the extracellular electric field. This assumption is more realistic and biological compared to the "classic" assumption which is based on current source densities per unit volume because real current sources are caused by the opening or closing of membrane conductances in neurons. Note that these two different points of view can be complementary if we assume that the volumic density of current source I_m is

$$I_m = -\frac{\partial \rho}{\partial t}\ .$$

In this case, the two points of view are mathematically equivalent. This is the reason why we wrote the source term as $-\frac{\partial \rho}{\partial t}$ in Eq. 1.

An important assumption of the present formalism is that all observable phenomena can be modeled by fields which are twice differentiable (class C^2). While most fields will obey this criterion, it will considerably simplify the mathematical analysis to its simplest expression (commuting spatial and temporal first-order derivatives). In mean-field physics, by virtue of the Stone-Weierstrass theorem, it is always possible to make a uniform-convergence approximation of the

observable phenomena by a mean-field model of class C^2. Indeed, because the mean-field of a discontinuous field of first kind is necessarily a continuous field (the primitive of a discontinuous function of first kind is continuous), this restriction to class C^2 fields will not limit the applications of the theory developed here. Moreover, the theory will remain general because most fields are class C^2 in practice. It will not apply to very particular models, such as fields involving surfaces with infinitely small thickness, current sources without volume, fields that necessitate infinite energies[22]

Finally, the formalism developed below is only valid for well-defined ranges of spatial and temporal scales. We will consider scales greater than $1\ \mu m$ (about 300 times the size of ions such as K^+ or Na^+, including solvatation). This scale is chosen large enough for classic electromagnetism theory to apply without ambiguity (although in principle it can apply to scales down to a few nm). We will define as "microscopic", scales of the order of 1 μm, while "macroscopic" scales will be of the order of 50 μm or more. We will also consider the typical range of frequencies of electrophysiological signals, up to $10\ kHz$, for which the quasistatic approximation is valid.

B. Mean-field Maxwell theory

We start from Maxwell equations where we consider the spatial averages of the fields and electric parameters, which will be denoted here by brackets $< ... >$. The spatial average is made over some reference volume, which is invariant. Because of the scale invariance of Maxwell equations (e.g., see [8], chapter 4), the spatial averages of electric field $\vec{E}$, electric displacement $\vec{D}$, magnetic induction $\vec{B}$ and magnetic field $\vec{H}$ are linked by the following linear operatorial equations:

$$\begin{aligned} \nabla\cdot <\vec{D}> &= <\rho^{free}> & \nabla\cdot <\vec{B}> &= 0 \\ \nabla\times <\vec{E}> &= -\tfrac{\partial <\vec{B}>}{\partial t} & \nabla\times <\vec{H}> &= <\vec{j}> + \tfrac{\partial <\vec{D}>}{\partial t} \end{aligned} \tag{2}$$

where $<\vec{j}>$ and $<\rho^{free}>$ are the spatial averages of the current density and free charge density, respectively.

These equations allow one to find the general regularities that all models must satisfy. For example, the laws of energy conservation and momentum conservation can be deduced from this set of equations [8]. In particular, by using the relation $\nabla\cdot(\nabla\times\vec{C}) = 0$ (which is in general true for all vectorial fields of class C^2), one can deduce the differential law of charge conservation:

$$\nabla\cdot(\nabla\times <\vec{H}>) = \nabla\cdot <\vec{j}> + \nabla\cdot\frac{\partial <\vec{D}>}{\partial t} = \nabla\cdot <\vec{j}> + \frac{\partial\nabla\cdot <\vec{D}>}{\partial t} = \nabla\cdot <\vec{j}> + \frac{\partial <\rho^{free}>}{\partial t} = 0 \tag{3}$$

However, because the above equations relate the spatial averages of interaction fields ($\vec{E},\vec{D},\vec{B},\vec{H}$) with the spatial averages of the two matter fields ($\vec{j},\rho^{free}$), it is necessary to complete them with a specific physical model to apply them to a given biological medium. This specific model must allow measuring spatial averages at a scale which is determined by the measurement method (type of electrode for example). Thus, the measurement system determines a minimal reference volume, which necessarily implies to use a mean-field formalism.

In general, (for all media of class C^2), the fields $<\vec{E}>$, $<\vec{D}>$, $<\vec{H}>$ and $<\vec{B}>$ are linked by the following general equations:

$$\begin{aligned} <\vec{D}^*>(\vec{r},t) &= \int_{-\infty}^{+\infty} <\varepsilon>(\vec{r},\tau,\vec{E},\vec{H})\ <\vec{E}>(\vec{r},t-\tau)\,d\tau + <\vec{C}>(\vec{r},t,\vec{E},\vec{H}) \\ <\vec{B}>(\vec{r},t) &= \int_{-\infty}^{+\infty} <\mu>(\vec{r},\tau,\vec{E},\vec{H})\ <\vec{H}>(\vec{r},t-\tau)\,d\tau \end{aligned} \tag{4}$$

where μ and ε are respectively the absolute magnetic permeability and absolute electric permittivity tensors. Here, we have defined $<\vec{D}^*> = <\vec{D}> + <\vec{C}>$ where $<\vec{C}>$ is the source field resulting from conductance variations. Note that in classic electromagnetism, one defines the electric displacement relative to vacuum permittivity ε_∞ by $<\vec{D}_\omega> = \varepsilon_\infty <\vec{E}_\omega> + <\vec{P}_\omega>$ (in frequency space)[23], which expresses the fact that the polarization field is

proportional to the electric field through electric susceptibility $< \chi_\omega >$ ($< \vec{P}_\omega > \; = \; < \chi_\omega >< \vec{E}_\omega >$). It follows that $< \vec{D}^*_\omega > \; = \; < \varepsilon_\infty >< \vec{E}_\omega > + < \vec{P}_\omega > \; + \; < \vec{C}_\omega > = \; < \varepsilon_\omega >< \vec{E}_\omega > + < \vec{C}_\omega >$.

Considering Maxwell-Gauss' law ($\nabla \cdot < \vec{D} > \; = \; < \rho^{free} >$) and the definitions of the interaction fields imply the following relations between charge density and interaction fields:

$$\begin{cases} \nabla \cdot < \vec{D}^* > \; = \; < \rho_e^{free} > \\ \nabla \cdot < \varepsilon_\infty >< \vec{E} > \; = \; < \rho_e^{free} > + < \rho^{\Delta \; cond} > + < \rho^{bound} > \\ \nabla \cdot < \vec{P} > \; = \; - < \rho^{bound} > \\ \nabla \cdot < \vec{C} > \; = \; - < \rho^{\Delta \; cond} > \end{cases} \tag{5}$$

where $< \rho^{\Delta \; cond} >$ represents the average variation of free charge density produced by conductance variations, and $< \rho_e^{free} >$ is the average free charge density which does not result from membrane conductance variations. Note that the divergence of the field $< \vec{C} >$ depends on the exact mechanism of conductance variation. If this mechanism does not produce monopoles, then this divergence is zero. Also note that the field $< \vec{C} >$ is generally assumed to be independent of the field $< \vec{E} >$, which is a valid assumption for biological media in general, except if ephaptic interactions must be taken into account.

We also have

$$< \vec{\jmath} > (\vec{r}, t) = \int_{-\infty}^{+\infty} < \sigma^e > (\vec{r}, \tau, \vec{E}, \vec{H}) \; < \vec{E} > (\vec{r}, t - \tau) \, d\tau + < D > \; \nabla < \rho^{free} > . \tag{6}$$

where σ^e is the electric conductivity and $< D >$ is the mean ionic diffusion tensor [24]. We define $< D >$ as follows:

$$< D > \sum_{i=1}^{N} \nabla < \rho_i^{free} > = \sum_{i=1}^{N} < D_i > \nabla < \rho_i^{free} >$$

where the sums run over the different ionic species. Thus, we can write that the part of current density caused by concentration changes equals $< D > \nabla < \rho^{free} >$[25]. In expression (6), we have separated the current produced by ionic diffusion from the current produced by other physical causes such as Ohm's effect, polarization, etc. Note that this separation was made here for simplicity, but it is also possible to integrate diffusion effects in the expression of the mean conductivity (see Eq. A4 in Section A 1).

It is important to note that the first term in the righthand side of Eq. 6 is not exclusively due to Ohm's law (which relates to energy dissipation), but can reduce to it in some cases [7, 10]. In general, Eq. 6 gives a time-dependent electric conductivity (or frequency-dependent in frequency space), which is not the case for Ohm's law in general (see Appendix A 3). Also note that the integrals in Eqs. 4 and 6 can be seen as convolution products relative to time, in which case they take the form of a simple product in frequency space.

Thus, according to this theory, it is sufficient to model the physical and geometrical nature of the extracellular medium by using electromagnetic parameters and diffusion coefficients to simulate the interaction fields when the current sources are known – this is usually called the *forward problem*. Inversely, we can also deduce the physical characteristics of the sources from the knowledge of the electromagnetic parameters and interaction fields, as well as their spatial and temporal variations – this is known as the *inverse problem*.

Finally, the integrals in Eqs. 4 and 6 must satisfy the causality principle, according to which the future cannot determine the present state of the system. For example, the value of electric field $< \vec{E} >$ at time $t + |\Delta t|$ must not influence the value of electric displacement $< \vec{D} >$ at time t. Thus, the causality principle determines a supplementary constraint on the possible values of tensors $< \mu >$, $< \varepsilon >$ and $< \sigma^e >$, which limits the number of possible mathematical models of the extracellular medium. For instance, as detailed below in Section II F, this principle imposes mathematical relations between the electric parameters $< \varepsilon >$ and $< \sigma^e >$, which are called Kramers-Kronig relations for linear media.

The set of equations above define a mean-field formalism in which Maxwell equations are formulated with spatial averages. In the next sections, we consider different approximations to this formalism.

C. The quasi-static approximation in mean field

The first approximation to the Maxwell equations is the *quasi-static approximation*, which consists of de-coupling electric and magnetic variables. In general, the time variation of $<\vec{B}>$ produces an electric field $<\vec{E}>$ (Lenz-Faraday effect), the electric and magnetic variables are coupled in Maxwell equations (Eq. 2) by the following expression:

$$\nabla\times<\vec{E}> \;=\; -\frac{\partial<\vec{B}>}{\partial t} \tag{7}$$

It was shown that for biological media and current sources, the Lenz-Faraday effect is negligible [11]. In such conditions, we can write:

$$\nabla\times<\vec{E}> \;=\; 0 \tag{8}$$

Under this quasi-static approximation, the electric and magnetic variables are de-coupled in Maxwell equations, and the electric field obeys:

$$<\vec{E}> \;=\; -\nabla<V>$$

This approximation is also called the *a priori* quasistatic approximation, by opposition to the *a posteriori* quasistatic approximation, which consists of finding the general solution of Maxwell equations and later de-couple the electric and magnetic variables (see details in [11]). Although these two approximations are not strictly equivalent, we will only consider the *a priori* quasistatic approximation in the remaining of this paper.

According to this approximation, Maxwell equations simplify to the following expressions:

$$\begin{cases} \nabla\cdot<\vec{D}> \;=\; <\rho^{free}> \\ \nabla\times<\vec{E}> \;=\; 0 \\ \nabla\cdot<\vec{\jmath}> + \frac{\partial<\rho^{free}>}{\partial t} \;=\; 0 \end{cases} \tag{9}$$

where the current density $<\vec{\jmath}>$ is linked to the electric field $<\vec{E}>$ by Eq. 6. Note that, contrary to the static cases (electrostatics and magnetostatics), the fields $<\vec{E}>$, $<\vec{D}>$, $<\vec{\jmath}>$ and $<\rho^{free}>$ are here space and time-dependent.

In the following, we consider the complex Fourier transform

$$X_\omega = \int_{-\infty}^{+\infty} X(t)\, e^{-i\omega t} dt \quad , \quad X(t) = \frac{1}{2\pi}\int_{-\infty}^{+\infty} X_\omega\, e^{i\omega t} d\omega$$

where $\omega = 2\pi f$. Note that because of the linearity of the spatial average, we have $<\vec{X}>_\omega = <\vec{X_\omega}>$.

Applying the complex Fourier transform to Eqs.4, 6 and 9 leads to:

$$\begin{cases} \nabla\cdot(<\varepsilon_\omega>\nabla<V_\omega>) \;=\; -<\rho_{e\omega}^{free}> + \nabla\cdot<\vec{C}_\omega> \\ \nabla\cdot(<\sigma_\omega^e>\nabla<V_\omega>) \;=\; i\omega<\rho_{e\omega}^{free}> \;-\; i\omega\,\nabla\cdot<\vec{C}_\omega> + \nabla\cdot(<D>\;\nabla<\rho_\omega^{free}>) \end{cases} \tag{10}$$

The first of these equations is Poisson's law in mean-field. Although in some cases (electrostatics), the Poisson equation is sufficient to determine the solution of the system, it is not sufficient in the quasistatic case, and the second equation is necessary to close the system. This second equation is the differential law of charge conservation (in the presence of diffusion) and takes into account the time variations of the electric potential

By multiplying the first equation of Eqs. 10 by $i\omega$, and adding the result to the second equation, leads to:

$$\nabla^2 < V_\omega > + \frac{\nabla < \gamma_\omega >}{< \gamma_\omega >} \cdot \nabla < V_\omega >= \frac{1}{< \gamma_\omega >} \nabla \cdot (< D > \nabla < \rho_\omega^{free} >) \tag{11}$$

where $\gamma_\omega =< \sigma_\omega^e > +i\omega < \varepsilon_\omega >$ is the admittance of the extracellular medium. This equation is general and can be used to calculate the extracellular potential in an extracellular medium with arbitrarily complex properties (i.e., when the electric parameters depend on frequency and space). It is a generalization of expressions obtained previously [6, 7]. The righthand term accounts for ionic diffusion.

Because Maxwell equations are scale invariant, the expression above (Eq. 11) is valid at all scales. Like in any mean-field approach, the spatial scale can be chosen according to the scale of the phenomenon that needs to be modeled, as well as the physical size and distance between electrodes. For example, in the case of CSD of mammalian cerebral cortex, one must consider scales of the order of 50 μm to resolve the field produced by each cortical layer.

Note that in the quasistatic approximation, the explicit dependence of the electric field on magnetic permeability μ completely disappears. However, there can still be an implicit dependence through $\vec{H}$ in nonlinear media, because the electric field does not depend explicitly on magnetic induction anymore.

D. The quasistatic approximation at larger scales

At small scales ($\approx 1\ \mu$m), biological media such as the cerebral cortex are far from homogeneous and isotropic. The electric parameters can display large variations, for instance between fluids and membranes. However, at larger scales ($\approx 50\ \mu$m), such media can be considered as homogeneous and isotropic. In such a case, the tensors $< \varepsilon_\omega >$ and $< \sigma_\omega^e >$ can reduce to scalar quantities. Note that the fact of considering larger scales suppresses the directional dependence of the propagation of currents by a statistical equivalent, without changing the frequency dependence produced by physical phenomena at small scales. The transition from small scales to larger scales gives the same form as Eqs. 11, but with scalar parameters which will have an explicit dependence on space, frequency and the values of the field in general[26]. The rate of spatial variation of these parameters at scales of the order of 50 μm is approximately zero, such that:

$$\begin{cases} \nabla < \sigma_\omega^e > |_{10^6\ \mu m^3} \approx 0 \\ \\ \nabla < \varepsilon_\omega > |_{10^6\ \mu m^3} \approx 0 \end{cases} \tag{12}$$

Note that there can be a frequency dependence of the current propagation which results from microscopic inhomogeneities of the electric parameters [6], from polarization phenomena [10] or from ionic diffusion [7]. This frequency dependence of the current will not disappear when considering larger scales. On the other hand, new frequency dependencies may appear, such as for example the transformation of a frequency-independent conductivity tensor at small scales ($\sim 1\ \mu$m) to a scalar conductivity at large scales ($\sim 50\ \mu$m) will be associated to a frequency dependence of this macroscopic conductivity (for details, see [7]). In agreement with this, measurements of the macroscopic conductivity demonstrated strong frequency dependence in different biological tissues [12].

E. The linear approximation in mean-field

Still within the quasistatic approximation, we now consider the further simplification that the extracellular medium is *linear*. In a linear medium, the electric parameters are independent of the values of the fields (note that this linearity is different than that of Maxwell equations, which are always linear). In this case, the electric parameters only depend on space and time (or space and frequency).

In this case, the system of equations (10) becomes linear at small scales. This linear approximation is easy to justify for the magnetic field, given the small currents involved (for example, $4\pi \times 10^{-7}\ H/m$ in neocortex) and the gradient of μ is almost zero (see [13]). In contrast, the linear approximation is less trivial in the case of the electric field because of the many nonlinearities involved. For example, several ionic conductances are strongly voltage-dependent (such as

the Na^+/K^+ conductances involved in action potentials), which will make the electric parameters of membranes strongly dependent on the electric field. Nevertheless, the total volume of tissue occupied by membranes is small compared to other regions where the linear approximation is valid, so biological tissues can in general be considered as linear. Note that this linearity is evident for low frequencies (<10 Hz), but it is less evident for high frequencies (>100 Hz), where nonlinear phenomena such as action potentials can have a major contribution.

F. The Kramers-Kronig relations under the linear approximation

As discussed above in Section II B, the causality principle determines a supplementary constraint on the possible values of tensors $< \mu >$, $< \varepsilon >$ and $< \sigma^e >$. In the linear approximation, one can show that, in general (for isotropic media of class C_2), the linking equation between the electric displacement and electric field takes the following form:

$$\vec{D}(\vec{x},t) = \vec{E}(\vec{x},t) + \int_0^\infty f(\vec{x},\tau)\vec{E}(\vec{x},t-\tau)\,d\tau \tag{13}$$

In this case, one can show that the frequency dependence of electric parameters is not arbitrary but is linked by the Kramers-Kronig relations (see Section 82 in [14]):

$$\begin{aligned} \varepsilon_\omega(\vec{x}) - \varepsilon_\infty(\vec{x}) &= \frac{2}{\pi} \fint_0^\infty \frac{\sigma^e_{\omega'}(\vec{x}) - \sigma^e_0(\vec{x})}{\omega'^2 - \omega^2}\, d\omega' \\ \sigma^e_\omega(\vec{x}) - \sigma^e_0(\vec{x}) &= -\frac{2\omega^2}{\pi} \fint_0^\infty \frac{\varepsilon_{\omega'}(\vec{x}) - \varepsilon_\infty(\vec{x})}{\omega'^2 - \omega^2}\, d\omega' \end{aligned} \tag{14}$$

where principal integrals ($\fint$) are used. ε_∞ is the absolute electric permittivity of vacuum and σ^e_0 is the static electric conductivity ($\omega = 0$). Note that these relations can be seen as a direct and inverse transform. The Maxwell-Wagner time $|\frac{\varepsilon_\omega}{\sigma^e_\omega}|$ represents the characteristic time (or "inertia") for settling into a stationary regime, and can be strongly frequency dependent [10]. Interestingly, this ratio is mathematically analogous to the time-frequency uncertainty principle in Fourier transforms when the electric conductivity of the extracellular medium becomes very small at zero frequency (see Appendix A 5). Note that there exists no such relation for the spatial variations of electric parameters, which are specific to each medium.

It is important to note that the Kramers-Kronig relations have a strong consequence on the plausibility of purely resistive media. If a medium is purely resistive, then both conductivity and permittivity are constant and independent of frequency. However, if one takes into account a very weak frequency dependence of conductivity ("quasi-resistive" media), such as $\sigma^e_\omega - \sigma^e_0 \sim f^\alpha$ with $\alpha << 1$, then the Kramers-Kronig relations impose that we necessarily have $\varepsilon_\omega - \varepsilon_\infty \sim f^{-(1-\alpha)}$. In such a case, the permittivity will be strongly frequency dependent, so will be the Maxwell-Wagner time $\tau_{MW} = |\frac{\varepsilon_\omega}{\sigma_\omega}|$. Thus, a purely resistive extracellular medium is a singularity, and is not likely to be realistic model for complex biological media.

III. APPLICATION OF THE QUASISTATIC MEAN-FIELD THEORY TO LINEAR MEDIA

In this section, we apply the theory outlined above to media which are linear in the electromagnetic sense, and which are homogeneous and isotropic (at macroscopic scales). This is equivalent to assume that the macroscopic parameters $< \sigma_\omega >$, $< \varepsilon_\omega >$ and $< D >$ are scalars independent of space, such that $\nabla(< \sigma_\omega > + i\omega < \varepsilon_{\omega>}) \approx 0$ and $\nabla < D > \approx 0$. This approximation is certainly valid for relatively large distances (greater than $\sim 50\,\mu m$). We also consider the system under the quasistatic approximation as defined above.

In the following sections, we examine different limit cases. The first case corresponds to the standard model with dipolar sources and a resistive (or quasi-resistive) extracellular medium. A second case will consider the same model, but with additional monopolar sources. The third case will consider ionic diffusion (not present in the two first cases), which also implies monopolar sources. In each case, we will derive the expression to use for CSD analysis.

A. Dipole sources in resistive and quasi-resistive media

We start with the standard model in which the electric conductivity of the extracellular medium is constant (in space and frequency), scale invariant, and isotropic. We also consider that diffusion is negligible. Under these hypotheses, we have $\nabla < \gamma_\omega >= 0$ (homogeneous and isotropic medium) and $< \gamma_\omega >= \bar{\sigma} = cst.$, and the general formalism (Eq 11) reduces to:

$$\nabla^2 < V_\omega > \; = 0 \tag{15}$$

We can also consider a slightly more realistic model of the extracellular medium by assuming that it is quasi-resistive ($< \sigma_\omega > \approx \bar{\sigma}$) instead of resistive ($< \sigma_\omega >= \bar{\sigma}$) (because the latter represents a singularity as outlined above in Section II F), isotropic and homogeneous for large scales ($\sim 50\ \mu$m; the medium is allowed to be non-homogeneous for smaller scales of the order of $\sim 1\ \mu$m). Note that in general, the non-homogeneity of conductivity at smaller scales can induce a frequency dependence at larger scales (see [6, 7]). Thus, the hypothesis that the macroscopic conductivity is independent of frequency is equivalent to assume that there is no significant variations of impedance at microscopic scales.

In such conditions, Eq. 11 again reduces to:

$$\nabla^2 < V_\omega > \; = 0 \tag{16}$$

In some formulations, the standard model does not consider the possibility of microscopic ($\sim 1\ \mu$m) monopolar sources [1, 3]. This is equivalent to hypothesize that, at every time, each portion of cell membrane has an equal number of positive and negative charges at opposite sides of the membrane, such that it is locally neutral. This hypothesis is also equivalent to state that the extracellular electric field is produced by dipoles (or more complex multipolar arrangements), and that the monopolar component of the field is negligible at scales of $\sim 1\ \mu$m[27]. This implies that the attenuation of the extracellular potential follows a law which varies as $1/r^2$ (or $1/r^3$, $1/r^4$ ... for multipoles of higher order) when $r \to \infty$, where r is the distance to the source. Thus, in the standard model, the electric displacement in frequency space (see Eqs. 4 and 5) is given by:

$$< \vec{D}^*_\omega > \; = \varepsilon_\infty < \vec{E}_\omega > + < \vec{P}_\omega > + < \vec{C}_\omega > \; = \; < \varepsilon_\omega >< \vec{E}_\omega > + < \vec{C}_\omega > \tag{17}$$

where

$$\begin{cases} \nabla \cdot < \vec{D}^*_\omega > \; = 0 \\ \nabla \cdot \varepsilon_\infty < \vec{E}_\omega > \; = \; + < \rho^{bound}_\omega > \\ \nabla \cdot < \vec{P}_\omega > \; = \; - < \rho^{bound}_\omega > \\ \nabla \cdot < \vec{C}_\omega > \; = 0 \end{cases} \tag{18}$$

at large scales ($\sim 50\ \mu$m). Taking the inverse Fourier transform, one obtains:

$$\nabla^2 < V > \; = 0 \tag{19}$$

According to this model, the inverse solution (CSD method) can be obtained assuming that the voltages measured at n different extracellular sites are solution of Laplace equation. According to the superposition principle, the extracellular potential can be considered as resulting from a sum of n macroscopic dipolar sources for sufficiently large n. Note that the value of n is determined by Shannon's sampling theorem, according to which the number of samples (number of electrodes n) must be twice larger than the larger spatial frequency of the field. To evaluate these n dipolar sources, one can simply apply the inversion of the matrix linking the n measured voltages with the n dipolar sources according to the

"forward" solution of Laplace equation (see e.g., [3]). Note that this approach is different than the classic CSD method proposed by Mitzdorf [1], which is based on a Poisson type equation.

The hypothesis of local neutrality in a homogeneous and isotropic extracellular medium implies that the frequency dependence of the measured signal is only due to the frequency dependence of the source (for example the effect of morphology – see [15], the exponential or bi-exponential nature of synaptic conductances, correlations in synaptic activity, action potentials, etc), because Laplace equation does not explicitly depend on frequency. Thus, according to the standard model, there is no filtering due to extracellular space and the power spectrum of the extracellular potential is identical to that of the current sources.

Finally, it is important to note that, in a resistive extracellular medium, if we express the extracellular potential as a function of the dipole moments instead of the current sources, then the power spectral density (PSD) of the electric potential will necessarily have a supplementary frequency dependence of the form $1/\omega^2$ compared to that of the current. This is due to the fact that the current is proportional to the temporal derivative of the the dipole moment $\vec{p}_\omega$ (defined from the charge distribution). However, the situation is different if the medium is quasi-resistive. In this case, the Kramers-Kronig relations give $\varepsilon_\omega \sim \frac{1}{\omega}$, and thus the ratio $\frac{\vec{p}_\omega}{\varepsilon_\omega}$ will have little frequency dependence. It follows that the PSD of the extracellular potential will have approximately the same frequency dependence as the current sources in a quasi-resistive medium. This is a striking difference between resistive and quasi-resistive media. As discussed above, the latter is a more realistic situation because any spatial variation of microscopic conductivity will necessarily induce a frequency dependence of the macroscopic conductivity (see [6]).

B. Monopolar sources in resistive and quasiresistive media

In the previous section, we hypothesized that the extracellular medium is locally neutral at microscopic scales ($\sim 1\,\mu$m), and thus, that the sources of the electric potential are dipoles. We now relax this hypothesis, and allow significant electric monopoles to appear in addition to conductance variations, so that the field results from both monopolar and dipolar contributions. Electric monopoles could result from different physical sources, such as the ionic selectivity of synaptic ion channels (similar to a "Maxwell Daemon"), combined with the finite velocity of charge movement [16]. These factors should create some accumulation of charge in the vicinity of the synapse when synaptic conductances are activated[28]. Note that monopoles are transient by definition, and equivalently, one could consider that the conductance variations determine a non-stationary regime $\nabla\cdot <\vec{j}> + \frac{\partial <\rho^{free}>}{\partial t} = 0$ (see Appendix A 2). In this transient regime, Kirchhoff's "point rule" does not apply (it is based on the law of current conservation $\nabla \cdot \vec{j} = 0$) and would apply only when the system reaches a stationary state. However, Kirchhoff's "loop rule" is always valid under the quasistatic approximation, because we have $\nabla \times \vec{E} = 0$, and consequently $\oint \vec{E} \cdot \vec{ds} = 0$, which is at the basis of the latter rule.

Contrary to the assumptions of the dipole model, monopolar sources imply that integrating the charge density over a closed surface surrounding each source is non-zero. To include the contribution of monopolar current sources, we have

$$I^n_\omega = \oiint_{\partial D} <\vec{j}_\omega> \cdot \hat{n}\, dS = \iiint_D \nabla\cdot <\vec{j}_\omega> dv = -i\omega Q_\omega \neq 0 \tag{20}$$

where Q_ω the total charge contained in the source. Note that this relation shows that the monopolar component is linked to the current through a temporal derivative, which is a consequence of the charge conservation law. Consequently, the extracellular potential (which is here proportional to the charge) will not have the same power spectrum as the source, and will have an additional $\sim \frac{1}{\omega^2}$ component for a resistive extracellular medium. However, similarly to the case of dipolar sources in previous section, the situation is different for a quasi-resistive medium. The Kramers-Kronig relations imply $\varepsilon_\omega \sim \frac{1}{\omega}$, and the ratio $\frac{Q_\omega}{\varepsilon_\omega}$ will have very little frequency dependence and the PSD of the extracellular potential will be very similar to that of the sources.

If we consider the same conditions as for the standard model (resistive or quasi-resistive media), we obtain

$$\begin{cases} \nabla\cdot < \vec{D}^{*}_{\omega} > &= < \rho^{free}_{e\omega} > \\ \nabla\cdot \varepsilon_{\infty} < \vec{E}_{\omega} > &= < \rho^{free}_{e\omega} > + < \rho^{\Delta\ cond}_{\omega} > + < \rho^{bound}_{\omega} > \\ \nabla\cdot < \vec{P}_{\omega} > &= - < \rho^{bound}_{\omega} > \\ \nabla\cdot < \vec{C}_{\omega} > &= - < \rho^{\Delta\ cond}_{\omega} > \end{cases} \tag{21}$$

In such conditions, Eq. 11 becomes:

$$\nabla^2 < V_{\omega} > \ = \ 0 \tag{22}$$

for resistive and quasi-resistive extracellular media. Thus, in temporal space, we have the same equation for both cases:

$$\nabla^2 < V > \ = \ 0 \tag{23}$$

However, if we take into account monopolar current sources and the law of charge conservation, then we have in general:

$$\sigma_{\omega}\nabla^2 < V_{\omega} > \ = \ i\omega < \rho_{\omega} > \tag{24}$$

where $\sigma_{\omega} = cst.$

Thus, the model with monopolar current sources has a different structure than the dipole model in Section III A because $< \rho_{\omega} > \neq 0$. Local neutrality in a homogeneous and isotropic extracellular medium implies an identical frequency dependence of the current source $I_{\omega} = -i\omega < \rho_{\omega} >$) and the extracellular potential. Like the standard model, there is no "filter" in this case. There is a notable difference, however. The law of attenuation with distance varies here in $1/r$ instead of $1/r^2$ for $r \to \infty$. If the number of electrodes is large enough to respect Shannon's sampling theorem, then the current source densities can be simply evaluated by approximating the Laplace equation using finite difference methods, as well as the knowledge of the "forward" solutions of this equation (see [3]). We will see in the next section that these conclusions are different if ionic diffusion is taken into account.

C. Models with ionic diffusion

While the influence of ionic diffusion was neglected in the previous sections, we now consider this case more explicitly without any other hypothesis about the medium. If a selective ion channel opens, the flow of ions may induce accumulation of charges in the region adjacent to the channel if ions diffuse faster than the time needed for passing through the channel (which will generally be the case). The electric field resulting from conductance variations is not selective on the type of ion, such that the positive ions are attracted and negative ions are repulsed if the field is negative (and *vice-versa* for a positive field). This is contrary to the flow inside the channel because it is selective to only a subset of ionic species. The combination of these factors makes it unavoidable that there will be charge accumulation around open ion channels. In the standard model, this charge accumulation is considered as negligible.

We now evaluate the consequences of this phenomenon on the frequency dependence of the field produced by ionic conductances in the subthreshold regime. If we consider a homogeneous extracellular medium with constant electric parameters (independent of frequency at large scales, $\sim 50\ \mu$m), then we have:

$$\begin{aligned} < \sigma^{e}_{\omega} > |_{M} &= \bar{\sigma} \\ < \varepsilon_{\omega} > |_{M} &= \bar{\varepsilon} \\ < D > |_{M} &= \bar{D} \neq 0 \end{aligned} \tag{25}$$

where the parameters $\bar{\sigma}$, $\bar{\varepsilon}$ and $\bar{D}$ do not depend on space.

According to those hypotheses, variations of ionic concentrations appear in the vicinity of the open ion channels, and these variations are opposite to the current produced by the electric field resulting from conductance variations. It thus appears that the conditions of current propagation at microscopic scales ($\sim$ 1 μm) cannot fulfill the condition of homogeneous ion concentration which is at the basis of Ohm's differential law (see Appendix A 3). In such conditions, the electric parameters of the extracellular medium have the following form at microscopic scales ($\sim$ 1 μm):

$$\begin{aligned} < \sigma_\omega^e > |_m(\vec{x}) &= \bar{\sigma}_m(\vec{x}) \\ < \varepsilon_\omega > |_m(\vec{x}) &= \bar{\varepsilon}_m(\vec{x}) \\ < D > |_m(\vec{x}) &= \bar{D}_m \neq 0 \end{aligned} \tag{26}$$

with

$$< \gamma_\omega > |_M = < < \gamma_\omega > |_m > |_M \tag{27}$$

This last equation is necessary to keep the consistency between microscopic ($\sim$ 1 μm) and macroscopic ($\sim$ 50 μm) scales.

According to this model, the current density (at microscopic scales, $\sim$ 1 μm) is given by:

$$< \vec{j} > |_m = -\bar{\sigma}_m \nabla < V > |_m + \bar{D}_m \nabla < \rho > |_m \tag{28}$$

where we have (see Eq. A11)

$$\bar{\sigma}_m = \lambda_q \tau_c n_v(\vec{x}, t) \tag{29}$$

This expression can be deduced by separating the domain into sufficiently small elements such that ion density can be considered as spatially homogeneous, and sufficiently large for Ohm's law to apply.

According to Boltzmann distribution (see Appendix A 1), we have

$$\nabla < \rho > |_m(\vec{x}, t) = \frac{< q >^2}{kT} n_v \nabla < V > |_m(\vec{x}, t) = \frac{< q >^2}{k \lambda_q \tau_c T} \bar{\sigma}_m \nabla < V > |_m \tag{30}$$

By taking into account Eqs. 28 and 29, we obtain

$$< \vec{j} > |_m = [\bar{D}_m - \frac{k \lambda_q \tau_c T}{< q >^2}] \nabla < \rho > |_m = < \beta > |_m \nabla < \rho > |_m \tag{31}$$

where $< \beta >$ is an effective diffusion coefficient. Note that the value of $< \beta >$ is smaller than the mean diffusion coefficient because $\frac{k \lambda_q \tau_c T}{< q >^2}$ must be positive. The value of $< \beta >$ also depends on the values of ionic concentrations because several parameters in Eq. 31 are concentration-dependent and is proportional to temperature because the ionic diffusion coefficient is itself proportional to temperature (see for example the Einstein relation for diffusion).

Applying the differential law of charge conservation, we get

$$< \beta > |_m \nabla^2 < \rho > |_m = -\frac{\partial < \rho > |_m}{\partial t} \tag{32}$$

Thus, the charge density produced in the vicinity of the ion channel is solution of a parabolic differential equation similar to the diffusion equation[29].

It follows that the charge density obeys:

$$\nabla^2 < \rho_\omega > |_m = -i \frac{\omega}{< \beta > |_m} < \rho_\omega > |_m \tag{33}$$

At microscopic scales ($\sim$ 1 μm), we obtain (see Eq. 11):

$$\nabla^2 < V_\omega > |_m + \frac{\nabla(< \gamma_\omega > |_m)}{< \gamma_\omega > |_m} \cdot \nabla < V_\omega > |_m = \frac{i\omega}{< \gamma_\omega > |_m} \cdot \frac{< D > |_m}{< \beta > |_m} < \rho_\omega > |_m \sim i\omega < V > |_m \tag{34}$$

Here, the proportionality between $< \rho_\omega >|_m$ and $< V_\omega >|_m$ can be deduced from the linear (first-order) approximation of Eq. A3 (see Appendix A 1). The second-order approximation would give a cubic term in $< V_\omega >|_m$.

Applying the consistency equation between scales by assuming the statistical independence of the parameters leads to the following equality:

$$\nabla^2 < V_\omega >|_M = -\frac{i\omega}{< \gamma_\omega >|_M} \cdot \frac{1}{< \beta >|_M} < \rho_\omega >|_M \tag{35}$$

with

$$\begin{aligned} \frac{1}{<\gamma_\omega>|_M} &= \frac{1}{N}\sum_{j=1}^{N} \frac{1}{<\gamma_\omega^j>|_m} \\ \frac{1}{<\beta>|_M} &= \frac{1}{N}\sum_{j=1}^{N} \frac{<D^j>|_m}{<\beta^j>|_m} \\ < D >|_M &= \frac{1}{N}\sum_{j=1}^{N} < D^j >|_m \end{aligned} \tag{36}$$

where N is the ratio between the reference volumes at macroscopic and microscopic scales (note that to simplify the formalism, we have approximated the macroscopic mean by a discrete summation over microscopic means). The second term of the lefthand side of Eq. 34 becomes zero at macroscopic scales (see consistency equation Eq. 27). Note that the means over parameters γ_ω and β_m are harmonic means, while the means over matter fields are arithmetic means.

Finally, by applying the inverse Fourier transform, we obtain (for Maxwell-Wagner times much smaller than unity):

$$\bar{\sigma}\, \nabla^2 < V >|_M = -\frac{1}{< \beta >|_M} \frac{\partial}{\partial t} < \rho >|_M \tag{37}$$

Thus, the CSD method in the presence of ionic diffusion takes a form which is very close to the Mitzdorf model [1], because we have one source term. However, there are two notable differences: first, the frequency dependence of charge density implies that the extracellular medium will be frequency dependent according to an impedance which varies as $1/\sqrt{(\omega)}$ (see Appendix A 4). Second, the extracellular potential attenuates with distance according to a Yukawa potential $\frac{e^{-k(\omega)r}}{r}$ instead of $\frac{1}{r^2}$, as in the standard model. In this case, we have

$$| < V_\omega >_m(r)| = | < V_\omega >_m(R)\, | \frac{Re^{-\frac{1}{2}\sqrt{\frac{\omega}{|<\beta>|_m|}}(r-R)}}{r} \tag{38}$$

Here, the extracellular potential is proportional to the charge density (see Eqs. A3, A14, and A15 in Appendix A 4) under the linear approximation and for a spherical source. It is interesting to note that the exponential term increases with frequency such that the extracellular medium favors the propagation of low frequencies (low-pass filter), as shown in Fig. 1). This type of attenuation law in Fourier space is also consistent with an exponentially-decaying impedance. If the frequency spectrum is narrow, one can replace ω by its maximal value $k = \frac{1}{2}\sqrt{\frac{max(\omega)}{|<\beta>|_m|}}$, which leads to an attenuation law for the potential as $\frac{e^{-k(r-r_o)}}{r}$. We can thus write that the electric field is approximately equal to $< \vec{E} >|_m = -\nabla < V >|_m = e^{-k(r-r_o)}(kr+1)\frac{1}{r^2}\hat{r}$. In a resistive medium, this leads to an electric resistivity given by $< \rho^e >_m = \frac{1}{<\sigma^e>|_m(r)} = \frac{4\pi}{I}e^{-k(r-r_o)}(kr+1)$ (note that the current $I = |\vec{j}|\, 4\pi r^2$ is conserved in a resistive medium, and the field is given by $< \vec{E} >|_m = < \vec{j} >|_m / < \sigma(r) >|_m$). Note that this particular distance profile of the potential was calculated by assuming that the medium is homogeneous (see Appendix A 4), which makes it applicable only at short distances from the membrane (of the order of 10 to 50 nm).

[———— Figure 1 here ————]

Finally, it is important to note that this frequency dependence cannot be removed because it is an effect of the feedback caused by ionic diffusion when ion channels open, and this is inherent to biological tissue. Because the PSD of the extracellular voltage is of the form $\sim \frac{1}{\omega}\, I(\omega)$ (see Eq. A15 in Appendix A 4), one can view the effect of ionic diffusion as a "1/f filter", as found previously [7].

D. Comparison between the different models

We now compare the different cases examined here. From the point of view of the differential equations involved, in the "standard" model based on dipoles, as well as with monopoles, the extracellular potential is solution of the Laplace equation, which is elliptic. In the third model with ionic diffusion, the extracellular potential is solution of a Poisson type equation where the source term is proportional to the time derivative of the voltage (under the linear approximation), which gives a parabolic equation. As outlined above, the diffusion model is closer to the monopole model (as diffusion can have monopolar effects) in a resistive extracellular medium, but leads to a fundamentally different mathematical form. The physical reason for this difference is that the ionic diffusion at the interface ion channel/medium increases the inertia of the system as a function of frequency.

At the point of view of the CSD analysis method, different algorithms must be used according to which model of the extracellular medium is assumed. In the two first cases, one must use a "forward" solution because Laplace equation is non invertible. In this case, it is necessary to explicitly include the distance dependence of the extracellular potential , which varies as $1/r^2$ for dipoles (for distances sufficiently large compared to the size of the dipole) and $1/r$ for the model based on monopoles. Note that if the distance to the sources is not large enough (compared to the typical size of the sources), or if the dipolar moments are very large compared to monopolar moments, then the attenuation will be closer to a linear combination of $1/r$ and $1/r^2$.

In the diffusive model, however, the approach is totally different because of the parabolic nature of the equations. In this case, it is enough to apply the Laplace operator to recover the sources. Two strategies are possible. First, one could simply apply Laplace operator on the extracellular voltage to yield estimates of the current source densities. Second, one could use a "forward" model and consider an attenuation law following a Yukawa potential $\frac{e^{-k(\omega)r}}{r}$ and apply the same procedure as for the other models.

Perhaps the most interesting aspect is that the three different models considered here have a different spectral signature. In the dipole model (or monopole model in a quasi-resistive medium), the PSD of the extracellular potential is identical to that of the sources. The resistive monopole and the resistive dipole model exert a filtering effect of $1/f^2$ type, whereas the diffusive model is equivalent to a $1/f$ filter. Thus, the frequency characteristics of the signal can serve as a criterion to determine the most appropriate model. For example, if the PSD of the extracellular voltage has $1/f$ structure, this automatically discards a pure monopole model, as well as dipole models in resistive or quasiresistive media, and would suggest diffusive type models.

E. Synthesis and applications to experimental data

In this section, we synthesize the theoretical developments provided here, and suggest a guide of how to apply them to experimental data. The generalization of the CSD method for different cases of current sources and type of extracellular medium, is summarized in Table 1. The table considers monopolar and dipolar current sources, as well as different types of resistive and non-resistive media.

To perform a CSD analysis by allowing non-resistive properties of the extracellular medium, we suggest the following procedure.

1. Estimate the type of extracellular medium from the power spectral structure of CSD signals. As detailed above (Sections III A, III B, III C, the type of medium (resistive, quasi-resistive, diffusive, etc) and type of current sources (monopolar, dipolar, etc) can be inferred from the power spectral structure of the extracellular potential. This analysis should be done on non-filtered data to set constraints on the possible combinations of sources type of medium.

2. Identify the correct CSD expression compatible with the type of source/medium inferred from power spectra. Table 1 summarizes the different cases considered here. The expression identified is then used to calculate the current sources from the extracellular potential recordings.

Source	Medium	ε_ω	σ^e_ω	$\frac{V_\omega}{I^S_\omega}$	Law
1-pole	res.	cst	cst	$\sim \frac{1}{r\omega}$	$\sigma^e_\omega \nabla^2 < V_\omega >= i\omega < \rho^{free}_\omega >$
	quasi-res.	$\sim \frac{1}{\omega}$	cst	$\sim \frac{1}{r}$	$\sigma^e_\omega \nabla^2 < V_\omega >= i\omega < \rho^{free}_\omega >$
	res.+dif.	$\sim \frac{1}{\sqrt{\omega}}$	$\sim \frac{1}{\sqrt{\omega}}$	$\sim \frac{e^{-f(\omega)(r-r_0)}}{r\sqrt{\omega}}$	$\nabla^2 < V_\omega >= -i\omega \frac{<D>\|}{<\gamma_\omega>\|<\beta>\|} < \rho^{free}_\omega >$
	gen.	ε_ω	σ^e_ω	gen.	$\nabla^2 < V_\omega > + \frac{\nabla <\gamma_\omega>}{<\gamma_\omega>} \cdot \nabla < V_\omega >= \frac{1}{<\gamma_\omega>} \nabla \cdot (< D > \nabla < \rho^{free}_\omega >)$
2-pole	res.	cst	cst	$\sim \frac{1}{r^2\omega}$	$\nabla^2 < V_\omega >= 0$
	quasi-res.	$\sim \frac{1}{\omega}$	cst	$\sim \frac{1}{r^2}$	$\nabla^2 < V_\omega >= 0$
	res.+dif.	$\sim \frac{1}{\sqrt{\omega}}$	$\sim \frac{1}{\sqrt{\omega}}$	$\sim \frac{e^{-f(\omega)(r-r_0)}}{r^2\sqrt{\omega}}$	$\nabla^2 < V_\omega >= 0$
	gen.	ε_ω	σ_ω	gen.	$\nabla^2 < V_\omega > + \frac{\nabla <\gamma_\omega>}{<\gamma_\omega>} \cdot \nabla < V_\omega >= 0$
Mitzdorf (2-pole)	res.	cst	cst	$\sim \frac{1}{r^2}$	$\sigma^e \nabla^2 < V >= -I_m$

TABLE I: Different generalizations of the CSD method. The table shows the mean-field equations for different types of media, and for monopolar or dipolar sources. The Mitzdorf model is shown apart, because it does not correspond to any of these mean-field scenarios. Abbreviations: res. ⇒ resistive homogeneous medium, quasi-res.⇒ quasi-resistive homogeneous medium, res. + dif. ⇒ resistive homogeneous medium + ionic diffusion, gen. ⇒ general (non-homogeneous, with spatial and frequency-dependent variations of electric parameters), 1-pole ⇒ monopole, 2-pole ⇒ dipole. Note that the frequency-dependence of the permittivity and conductivity are not independent but are linked by the Kramers-Kronig relations. The quantity $\frac{V_\omega}{I^S_\omega}$ is the ratio between the Fourier transform of the extracellular potential V_ω and the Fourier transform of each point current-source I^S_ω which produce the field (asymptotic solution, far from the sources). The function $f(\omega)$ in "res+dif" determines a Yukawa type potential (see Fig. 1).

IV. DISCUSSION

In this paper, we have formulated a series of generalizations of the CSD analysis method applicable to extracellular recordings in brain tissue. This generalization is based on a general theory that we derived and which aims at linking the extracellular potential with current source densities in the tissue. We have considered a mean-field version of Maxwell equations by considering the different fields as averages over some reference volume. By varying the size of this volume, one can apply the same theory to different scales. At microscopic scales ($\sim 1\ \mu$m and smaller), the theory must use the microscopic values for electric parameters (for example, the very different resistivities of fluids or membranes). For mesoscopic or macroscopic scales ($\sim 50\ \mu$m and larger), the theory can directly include the "macroscopic" measurements of conductivity and permittivity, as well as their possible frequency dependence if needed. Note that this mean-field approach takes into account the physical and biological properties of the sources, and thus is more general than previous approaches [7] which did not consider source densities.

We have examined different limit cases, such as a purely resistive extracellular medium with current sources consisting exclusively of dipoles, in which case the theory recovers the standard model. In this standard model, the mean-field theory shows that the electric potential must be solution of Laplace equation, such that the "classic" CSD approach of Mitzdorf [1] does not apply. To inverse the CSD in this model, one must apply the forward solutions of Laplace equation because the associated operator is non-invertible (see [3]). In resistive media, the extracellular potential must have an additional frequency dependence of $1/f^2$ relatively to that of the current. Interestingly, we found that Laplace equation remains valid for extracellular media which are quasi-resistive (where the electric parameters weakly depend on frequency). In

this case, the frequency dependence of the extracellular potential is similar to that of the current. A weak frequency dependence was indeed found in some experimental measurements of resistivity [17, 18], while other experiments [12] displayed a much more pronounced frequency dependence. With respect to the attenuation with distance, the standard model predicts an attenuation law as $1/r^2$, for both resistive or quasi-resistive media.

We also examined the case of monopolar sources. If such monopolar sources are present in addition to dipolar sources, within resistive or quasi-resistive media, then the CSD equation takes a slightly different form predicting that the potential will attenuate asymptotically with the inverse of distance ($1/r$), while the standard dipole model predicts a square dependence ($1/r^2$). With monopolar sources, the potential in the extracellular medium is also solution of Laplace equation, and thus the inverse algorithm of the CSD method does not apply identically as for dipoles. To find the inverse CSD, one proceeds similarly as the standard model by using the "forward" solution of Laplace equation. However, in this case the sources must be considered as a linear combination of terms varying as $1/r$ (monopoles) and $1/r^2$ (dipoles) in this forward solution.

As a third model, we examined the case of ionic diffusion within resistive or quasi-resistive media. In this case, the CSD takes a form very close to the "monopolar" CSD discussed above, but we found that charge density is frequency dependent according to a Warburg impedance in $1/\sqrt{(\omega)}$ (see Appendix A 4 and Section III C). This result is in agreement with a previous modeling study of extracellular potentials in the presence of ionic diffusion [7]. Another consequence is that, for spherical symmetry, the attenuation with distance follows a Yukawa potential $\frac{e^{-k(\omega)r}}{r}$, which decays faster than the different laws considered above for large enough frequency (see Fig. 1). This particular form is responsible for a low-pass filtering of the extracellular medium. Note that this form is obtained for spherical symmetry, but other forms may be obtained in different geometries.

It is important to note that the CSD theory was originally designed without specific hypotheses about the nature of current sources [2, 4, 5], other versions of the CSD theory clearly assumed that current sources are dipoles [1, 3]. Assuming dipolar sources is equivalent to assume that we have stationary current conditions at all scales. However, we show here (Appendix III B) that at small scales (synapses), such a stationary current condition is not necessarily met. A first possible source of monopolar effects is the inertia of charge movement along membranes together with ion-channel selectivity. Following the opening of ion channels, the flow of ions will entrain a re-equilibration of the charges adsorbed on both sides of the membrane. While this process is usually considered as instantaneous, together with neglecting ion-channel selectivity, these processes may have important consequences. Indeed, if one takes into account the fact that charges do not move instantaneously and ion-channel selectivity, this will necessarily create transient charge accumulation and monopoles. A similar effect will occur through ionic diffusion and electric field, at the interface between the ion channel and the extracellular medium, because ions diffuse faster than their mean passage time through the channel, which will also create charge accumulation and monopolar effects. Note that when this mechanism produces an external electric field which will contribute to the extracellular field (in addition to transmembrane currents). These effects will contribute to transient monopoles, during which Kirchhoff's node law will not apply. The fact that ions move considerably slower than electrons in a metal conductor will also participate to deviations from Kirchhoff laws. Whether this transient time is significant, and whether the system could be continuously "outside of equilibrium" due to sustained synaptic activity, should be investigated by future work.

In the diffusion model, one can directly use the Laplace operator to inverse the CSD, contrary to the other models. Taking into account ionic diffusion requires to revise the "forward" approach, because the attenuation law does not follow a $1/r^2$ law, but rather a Yukawa-type law while the extracellular medium is associated to a Warburg-type impedance. In a previous study, we showed that indeed a Warburg type impedance could account for the transfer function between intracellular and extracellular potentials [19] (for frequencies comprised between 3 and 300 Hz). It is also consistent with measurements of conductivity and permittivity [12] (but see [17]). Note that the linear approximation in the diffusion model is not valid for high values of the potential (larger than ~50 mV; see A 4), so this model applies well to subthreshold activity, but may need to be revised for action potentials. Similarly, corrections to the CSD given by the "forward" approach (see for example [21]) may also need to be reformulated for non-resistive media.

Thus, with respect to the paradox of the CSD method, as described in the introduction, our study suggests that it is naturally solved by taking into account ionic diffusion. This introduces an additional source term in the general equation for the electric potential (see Eq. 11). This additional term gives a Poisson type equation for the potential (instead of Laplace equation), similar to the classic CSD approach. Contrary to the cases with resistive and quasi-resistive media, the

classic algorithm of CSD inversion given by Mitzdorf [1] is applicable here. Thus, the results obtained with the classic CSD analysis are perfectly consistent with ionic diffusion because diffusion gives a source term which is very close to the phenomenological model of current source density introduced by Pitts and Mitzdorf [1, 2], but in a manner consistent with Maxwell-Gauss law. So, we conclude that the usual approach for CSD inversion, although paradoxical, should nevertheless give results equivalent to a model with ionic diffusion and consistent with Maxwell-Gauss law.

Finally, the few limit cases considered here are by no means exhaustive. For example, we neglected the Maxwell-Wagner time of the extracellular medium and the microscopic variations of impedance. The theory outlined here is general enough to include these effects if needed, which is another way to solve the paradox. For instance, considering phenomena such as "reactive" extracellular media, which react to the electric field (for example through polarization of cell membranes), can be done by taking into account the Maxwell-Wagner time of the medium (see details in [7, 10]). According to Gabriel et al. [12], the macroscopic electric permittivity becomes larger while macroscopic conductivity becomes smaller for smaller frequencies, when the electric field is imposed according to a well-defined direction. In these measurements, $\omega\tau_{MW} << 1$ for frequencies larger than 10 Hz, but $\omega\tau_{MW}$ may be considerably larger for lower frequencies [7], where electric polarization may play an important role. The second term in the lefthand side of Eq. 11 would then not be negligible anymore. Because this term can be considered as an additional source term (see [6]), similar to the case of diffusion, this also solves the paradox described in the introduction.

In conclusion, we have provided here a generalized CSD approach valid for more realistic properties of the extracellular medium, taking into account ionic diffusion or polarization effects, usually neglected in the standard CSD analysis [1, 3]. We found that including such effects may have deep consequences on the expression to be used for estimating current sources, and thus may also have consequences on the values of current sources estimated from experimental recordings. For example, the potential due to monopolar sources will decay slower than for dipoles, which will necessarily affect the recorded potential at the electrode. Similarly, considering "reactive" aspects of the extracellular medium by including a significant Maxwell-Wagner time leads to a different CSD expression, close to the form derived for ionic diffusion. Future work should apply these expressions to extracellular recordings in brain tissue, with the aim of identifying which of these phenomena are most consistent with experimental data.

Appendix A: Appendix

1. Impedance for systems with ionic diffusion

In this appendix, we consider ionic diffusion at the interface between ion channels and the extracellular medium, as well as at the interface with the cytoplasm. We use the quasistatic approximation (in the thermodynamic sense), which implies that the net charge density must be solution of a parabolic partial differential equation, as for pure diffusion phenomena. We will next consider system in spherical symmetry, in which case the impedance is equivalent to a Warburg impedance.

a. Ionic diffusion under the quasistatic approximation in the thermodynamic sense

The current density at microscopic scales obeys the equation:

$$< \vec{j} >|_m = -\bar{\sigma}_m \nabla < V >|_m + \bar{D}_m \nabla < \rho >|_m \tag{A1}$$

with (see Eq. A11)

$$\bar{\sigma}_m = \lambda_q \tau_c n_v(\vec{x}, t) \tag{A2}$$

Let us assume that the system is in a quasi-static case in the sense of thermodynamics. As shown by application of Maxwell distribution of velocity distribution and the principle of detailed balance [20], we can deduce the Boltzmann distribution for a field which varies infinitely slow. This approximation is valid here because the drift velocity of ions

under an electric field is much lower than the absolute velocity of ions (which is of the order of sound velocity). Within this quasistatic approximation, we can apply the Boltzmann distribution to obtain the number of ions per unit volume as a function of time and space:

$$n_v(\vec{x},t) \;=\; n_v^{\infty}\,[e^{+\frac{<q>|_m<V>|_m(\vec{x},\,t)}{kT}} + e^{-\frac{<q>|_m<V>|_m(\vec{x},\,t)}{kT}}]$$

when we assume that $V(\infty) = 0$ at infinite distance, where n_v^{∞} is the number of ions per unit volume at an infinite distance from the source ("far distance") and $< q >$ is the mean absolute charge. $k = 1.3806503 \times 10^{-23}\ J/\,^{\circ}K$ is the Boltzmann constant and T is the temperature in degrees Kelvin. It follows that the net charge density is related to the value of the electric potential according to:

$$< \rho >|_m(\vec{r},t) = n_v^{\infty} < q >|_m\,[e^{+\frac{<q>|_m<V>|_m(\vec{x},\,t)}{kT}} - e^{-\frac{<q>|_m<V>|_m(\vec{x},\,t)}{kT}}] \tag{A3}$$

where $< \rho >|_m(\vec{r}_1,t)$ is the average net charge density. Note that the $-$ sign in the second righthand term comes from the sign of the charge. Also note that this relation implies that the net charge density is zero at an infinite distance, and is linked to the electric potential by a nonlinear relation[30].

Applying the operator ∇ on the net charge density gives:

$$\nabla < \rho >|_m(\vec{x},t) = \frac{(< q >|_m)^2}{kT}\, n_v \nabla < V >|_m(\vec{x},t) = \frac{(< q >|_m)^2}{\lambda_q \tau_c kT} \bar{\sigma}_m \nabla < V >|_m \tag{A4}$$

Note that no such relation would be possible outside of the quasistatic approximation in the thermodynamic sense.

2. Non-stationary aspect of the electric field produced by membrane conductance variations

In this appendix, we show that if the transmembrane current is non-zero, this necessarily implies a charge variation at the interior of the compartment according to a non-stationary regime

$$\nabla \cdot \vec{\jmath} + \frac{\partial \rho}{\partial t} = 0$$

We define as "interior" the domain delimited by the inner surface of the cell membrane as indicated in Fig. 2. We will show that for different values of stationary current, the net charge inside a cable compartment is different from zero, and depends on the value of the current. Thus, when the current is variable, the system is necessarily in a non-stationary regime.

To demonstrate this, suppose that we have a current density $\vec{j}$ which is time independent and stationary, satisfying

$$\nabla \cdot \vec{j} = 0\ .$$

The amount of charge situated in the interior of the compartment strictly inside the compartment can be calculated from the integral of the electric field across a closed surface:

$$Q_{int} = \oiint_{\partial D} \varepsilon \vec{E} \cdot \hat{n}\, dS \;=\; \iint_{channel+axial} \varepsilon_c\, \vec{E} \cdot \hat{n}\, dS \;+\; \iint_{membrane} \varepsilon_m\, \vec{E} \cdot \hat{n}\, dS \tag{A5}$$

where the integral is made over a Gauss surface which goes through the middle of the membrane thickness, as indicated in Fig. 2. The surface also avoids ion channels (by surrounding them below their inner side). $\varepsilon = \varepsilon_c$ and $\varepsilon = \varepsilon_m$ are the electric permittivity of the cytoplasm and of the membrane, respectively.

Taking into account Ohm's differential law and stationary current condition, one obtains:

$$I = \iint_{channel+axial} \vec{j} \cdot \hat{n}\, dS \;=\; \iiint \nabla \cdot \vec{j}\, dv = \iint_{channel+axial} \sigma_c\, \vec{E} \cdot \hat{n}\, dS \;= 0 \tag{A6}$$

where σ_c is the electric conductivity of the cytoplasm. Because the capacitive impedance is infinite for $f = 0$, the surface integral over the membrane is zero, and we obtain:

$$Q_{int} = \iint_{membrane} \varepsilon_m \vec{E} \cdot \hat{n} dS \tag{A7}$$

because $\varepsilon_c \vec{E} = \frac{\varepsilon_c}{\sigma_c} \vec{j}$ when electric parameters are independent of space.

The cylindric symmetry together with the isopotentiality of the surface of the membrane compartment imply that this integral is non zero and depends on the value of the transmembrane current I_m. If we have two different transmembrane currents, then the values of the electric field inside the membrane are necessarily different and the values of Q_{int} are different too. In particular, if the current I_m is zero, this integral equals the negative charge that there can be inside the compartment at rest.

It follows that, if we have a variable transmembrane current, the interior charge varies to satisfy $\nabla \cdot \vec{j} = -\frac{\partial \rho}{\partial t} \neq 0$ because the membrane time constant τ_m is not negligible. This shows that the variation of current sources caused by membrane conductance variations have the properties of a non-stationary regime. Note that this non-stationarity requires to take into account the volume of the membrane compartment, and would not be present for point processes.

3. Ohm's law and frequency dependence

In this appendix, we show that Ohm's law implies that the ratio between potential and current does not depend on frequency for frequencies smaller than 10^4 Hz. The aim of the appendix is to show the physical bases of the model shown in Section III C.

Let us apply an electric field $\vec{E}$, independent of time and space, at time $t = 0$ and during a time interval ΔT, to a homogeneous aqueous solution (similar to salted water) at thermodynamic equilibrium. The field will accelerate every ion according to the following velocity law:

$$\vec{v}(t_f) = \vec{v}(t_i) + \frac{q_k}{m_q} \vec{E} \, (t_f - t_i) \tag{A8}$$

where t_i is the initial ion collision time and t_f its final collision time. If the field is applied during a time interval ΔT much longer than the typical collision time between two molecules (or ions), then the mean velocity of ions is given by:

$$< \vec{v}(t) >_{\Delta T} = < \vec{v}(t_i) >_{\Delta T} + \frac{q_k}{m_q^k} \vec{E} < t_f - t_I >_{\Delta T} = < \vec{v}(t_i) >_{\Delta T} + \frac{q_k}{m_q^k} \vec{E} \tau_c^k \tag{A9}$$

where τ_c^k the mean collision time of ion k, q_k the charge of ion k and m_k the mass of ion k. Note that the mean collision time for ions such as Na^+, K^+, Cl^-, Ca^{++} in sea water are approximately equal to $10^{-12} - -10^{-14}$ s for temperatures between 250 $^\circ K$ and 350 $^\circ K$ [20].

If the system is at thermodynamic equilibrium, we have $< v(t_i) >_t = 0$. It follows that the time average of the current density is given by:

$$< \vec{j} > = < \sum_{k=1}^{N} \frac{q_k^2 \tau_c^k}{m_q^k} n_v^k > \vec{E} \tag{A10}$$

where n_v^k is the number of ions of type k per unit volume. Because the quantities $\frac{q_k^2}{m_q^k}$, τ_c^k and n_v^k are statistically independent, we can write:

$$\sigma^e = \lambda_q \tau_c n_v \tag{A11}$$

where $\lambda_q = < \frac{q_k^2}{m_q^k} >_k$, $\tau_c = < \tau_c^k >_k$ and $n_v = N < n_v^k >_k$ are average values of the quantities $\frac{q^2}{m_q}$, τ_c and n_v for each type of ion.

Thus, this expression shows that the ratio between the time average of the current and the electric field does not depend on time when the time interval ΔT is much longer than the mean collision time between two molecules of the solution, because the number of collisions of each ion is very large.

Because the mean collision time is of the order of $10^{-12} - 10^{-14}$ s for a temperature included between 250 $^\circ K$ and 350 $^\circ K$ (see details in [20]), we can write that we have a very good approximation of a variable electric field by a piecewise constant function (staircase), with time intervals are much longer than the mean collision times. Then, the time average of the current density will be proportional to the applied field. We can therefore write that the ratio between mean current density and applied electric field does not significantly depend on the frequency of electric field – nor of time – for frequencies smaller than 10^4 Hz [31]. This approximation is called differential Ohm's law.

4. Ionic diffusion in spherical symmetry

To simplify the computation of Eq. 33, we consider a model with a spherical source, surrounded by a spherically-symmetric (or isotropic) extracellular medium with boundary condition and isopotential over the surface of the source. In this case, we have the following equality in Fourier space:

$$\frac{d^2 < \rho_\omega >|_m}{dr^2} + \frac{2}{r}\frac{d < \rho_\omega >|_m}{dr} + i\frac{\omega}{< \beta >|_m} < \rho_\omega >|_m = 0 \tag{A12}$$

The general solution of this equation is:

$$< \rho_\omega >|_m(r) = A(\omega)\frac{e^{\sqrt{-i\frac{\omega}{<\beta>|_m}}\, r}}{r} + B(\omega)\frac{e^{-\sqrt{-i\frac{\omega}{<\beta>|_m}}\, r}}{r} \tag{A13}$$

where r is the distance between the geometric center of the source. Because we must have no charge accumulation at infinite, we must set $A = 0$, which gives:

$$< \rho_\omega >|_m(r) =< \rho_\omega >|_m(R)\frac{Re^{-\sqrt{-i\frac{\omega}{<\beta>|_m}}\,(r-R)}}{r} \tag{A14}$$

Taking into account Eq. 31, the current density is given by:

$$< j_\omega >|_m(r) =< \beta >|_m \frac{\partial < \rho_\omega >|_m}{\partial r} =< \beta >|_m \left(\frac{1}{r} + \sqrt{-i\frac{\omega}{< \beta >|_m}} \right) < \rho_\omega >|_m(r) \tag{A15}$$

By developing the net charge density (see Eq. A3) in Taylor series, we have at first order:

$$< \rho >|_m(\vec{x}, t) = n_v^\infty \; < q >|_m \left[e^{+\frac{<q>|_m <V>|_m(\vec{x},\, t)}{kT}} - e^{-\frac{<q>|_m <V>|_m(\vec{x},\, t)}{kT}}\right] \approx 2\frac{(< q >_m)^2\, n_v^\infty}{kT} < V >|_m(\vec{x}, t) \tag{A16}$$

At physiological temperature ($310\, ^oK$), we can write that the precision of this linear approximation is larger than 90 % if the potential is smaller than 15 mV (these estimates are obtained by replacing Boltzmann constant by the values of the mean charge, $\approx 2 \times 10^{-19}$ C). However, the precision drops to about 8 % for 100 mV, in which case one must consider up to the third-order term ($\sim < V >|_m^3$) in the Taylor expansion. This is the case for action potentials, and thus the propagation of the field will become more complex for spikes.

It follows that the impedance between infinite distance and a given point P at distance r from the source is given by:

$$Z_\omega(r) = 2\frac{kT}{(< q >|_m)^2 < \beta >|_m\, n_v^\infty}\frac{1}{(\frac{1}{r} + \sqrt{-i\frac{\omega}{<\beta>|_m}})} \tag{A17}$$

Thus, the impedance will tend to a Warburg impedance for large distances from the sources, and for high frequencies. Moreover, if the curvature radius is very large, or for planar membranes, one can set $R = \infty$, which gives:

$$Z_f \approx 2\frac{kT}{(< q >|_m)^2 < \beta >|_m\, n_v^\infty}\frac{1}{(\sqrt{-i\frac{\omega}{<\beta>|_m}})} = \frac{C}{\sqrt{\omega}} \tag{A18}$$

where $C \sim (1-i)$ and thus, the phase of the impedance becomes independent of frequency.

One sees that the value of the parameter $<\beta>|_m$ and the curvature radius determine the magnitude of the phase. They also determine the distance at which the impedance becomes equivalent to a Warburg impedance. For example, the estimates of impedance in rat cortex made previously [19] indicate that the impedance can be well approximated by a Warburg impedance for frequencies above 3 Hz.

5. Kramer-Kronig relations

In this appendix, we show that the Maxwell-Wagner time $\tau_{MW} = \frac{\varepsilon_\omega}{\sigma_\omega^e} \approx \frac{k}{\omega}$ when the conductivity is very low at zero frequency, based on Kramers-Kronig relations (see Eq. 14).

These relations show that if σ_ω^e does not depend on frequency, then ε_ω will also be frequency independent. These relations also show that if $\varepsilon_\omega - \varepsilon_\infty = k\omega^{-(1-b)}$, then we have (see Eq. 14)

$$\sigma_\omega^e - \sigma_0^e = \frac{-2\omega^2}{\pi} \fint_0^\infty \frac{k(\omega')^{-(1-b)}}{\omega'^2 - \omega^2}\, d\omega'$$

By setting $x = \frac{\omega'}{\omega}$, we obtain

$$\sigma_\omega^e - \sigma_0^e = \Big[\frac{-2}{\pi} \fint_0^\infty \frac{1}{x^{1-b}(x^2-1)} dx\Big] k\omega^b = k_1 k\omega^b$$

where we have by definition

$$k_1 = \fint_0^\infty \frac{1}{x^{1-b}(x^2-1)} dx = \lim_{|\epsilon|\to 0}\Big[\int_0^{1-|\epsilon|} \frac{1}{x^{1-b}(x^2-1)} dx + \int_{1+|\epsilon|}^\infty \frac{1}{x'^{1-b}(x'^2-1)} dx'\Big]$$

By replacing $x = 1/x'$ in the second integral in the righthand term, we get

$$k_1 = \lim_{|\epsilon|\to 0} \int_0^{1-|\epsilon|} [x^{-(1-b)} + x^{(1-b)}] \frac{1}{(x^2-1)} dx$$

This relation shows that we have $\frac{\varepsilon_\omega - \varepsilon_\infty}{\sigma_{\omega'}^e - \sigma_0^e} = \frac{1}{k_1\omega} = \frac{\kappa}{\omega}$ (we have set $\kappa = \frac{1}{k_1}$) such that a small variation of σ_ω relative to frequency (for low frequencies) will entrain a strong variation of ε_ω relative to frequency, and thus a very large value of τ_{MW} for low frequencies. If $\sigma_0^e \approx 0$ and if ε_ω is much larger than that of vacuum, then τ_{MW} is given by:

$$\tau_{MW} = \frac{\varepsilon_\omega}{\sigma_\omega^e} \approx \frac{\kappa}{\omega}. \tag{A19}$$

where κ is a constant which depends on the exponent b (see Fig. 3). This approximation corresponds well to the experimental measurements of *Gabriel et al* (see [12]).

Finally, if the conductivity varies very slowly with respect to frequency (small value of a), then the permittivity will be proportional to $1/\omega$, and will therefore vary very steeply at low frequencies.

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[22] In such particular cases, the partial and first-order derivatives of fields $\vec{E}$, $\vec{D}$, $\vec{B}$ and $\vec{H}$ are not defined for every point of space and time.

[23] $\vec{E}$ is the effective electric field and the polarization field $\vec{P}$ is produced by polarization of molecules and cell surface polarization. In general, the relation between these vectors is algebraic in Fourier space, and thus a convolution integral in temporal space.

[24] Because the law of ionic diffusion is given by $\vec{j}_{mat} = -D\nabla C$ when the units of C are mol/m^3 and when we have only one type of ion, we have multiplied the expression of $\vec{j}_{mat}$ by $-zF$ to yield the electric current density $\vec{j} = D\nabla\rho$ associated to each ionic species. z is the valence of the ions considered, and $F = 9.65 \times 10^4\ C/mol$ is the Faraday constant. The choice of the sign is according to the standard convention. Note that if the fundamental charge is taken as that of the proton, then one must multiply by the factor zF, but if it is that of the electron, then the multiplying factor is $-zF$.

[25] Note that the spatial average of $< D >$ will have similar values for different ionic species because the diffusion coefficients of the main ions (k^+, Na^+, Cl^-, Ca^{++}) have similar values for biological tissues in physiological conditions (see [9])

[26] Note that the space dependence is much smaller than the large variations seen at microscopic scales, for example between fluids and membranes.

[27] Note that one cannot say that the monopolar component is rigorously zero, because there is at least a monopolar component in the ion channels themselves, because of ion selectivity.

[28] Note that it is important here to take into account the *spatial extent* of the synapse, contrary to the standard theory where synapses are considered as point processes.

[29] Note that the coefficient $< \beta > |_m$ depends on ion concentrations via λ_q, $< q >^2$ and τ_c, and thus could vary greatly according to the activity of the surrounding neurons.

[30] A consequence of this nonlinear relation is that the medium will become nonlinear for high values of the electric potential.

[31] In fact, experiments have shown that the frequency of the signal much reach the order of 10^9–10^{10} Hz to evidence a deviation

between the measurements and the formalism given here (see details in De Felice L.J. 1981. *Introduction to Membrane Noise*, Plenum Press, New York; see also ref. [20]).

Figure legends

FIG. 1: (color online) Attenuation profile of the extracellular potential as a function of distance. The profile of the potential with distance is shown for two positive values of $< \beta >$: one value comparable to the diffusion coefficients of k^+, Na^+, Cl^- (left), and another value 100 times smaller (right). When $< \beta >$ is comparable to the diffusion coefficients, the attenuation according to Yukawa potential is similar to Coulomb's potential and we have a Warburg impedance. For smaller values of $< \beta >$, the Yukawa potential determines a significant additional low-pass filter. The attenuation law is very steep for frequencies larger than 100 Hz when $< \beta > |_m = 10^{-11}\ m^2/s$. The different curves indicated are the Coulomb's attenuation law as $1/r$ (monopol¡es; solid line) and as $1/r^2$ (dipoles; dotted line; thick gray lines correspond to attenuation according to a Yukawa potential; thin lines correspond to Yukawa attenuation combined with a Warburg impedance, which is the most complete case taking into account ionic diffusion effects. In each case, different frequencies are compared (1, 10, 100 and 1000 Hz) and are shown by different colors and dashed lines, as indicated. The current source has a radius of $5\ nm$.

FIG. 2: (color online) Scheme of an isopotential membrane compartment with ion channels. The blue circles indicate ion channels in the membrane. The dotted line indicates a Gauss surface delimiting the interior of the compartment. The values of electric permittivity ε are equal to ε_m in the membrane and ε_c in the cytoplasm. The electric conductivity σ is equal to σ_c in the open channels, and is assumed to be zero in the membrane.

FIG. 3: Representation of κ as a function of the exponent b. The values of κ were calculated from expression $\frac{1}{\frac{2}{\pi}\int_0^\infty \frac{1}{x^{1-b}(x^2-1)}dx}$, where $\int_0^\infty \frac{1}{x^{1-b}(x^2-1)}dx = lim_{x\to 1}\int_0^x [x^{-(1-b)} + x^{(1-b)}]\frac{1}{(x^2-1)}dx$.

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Figures

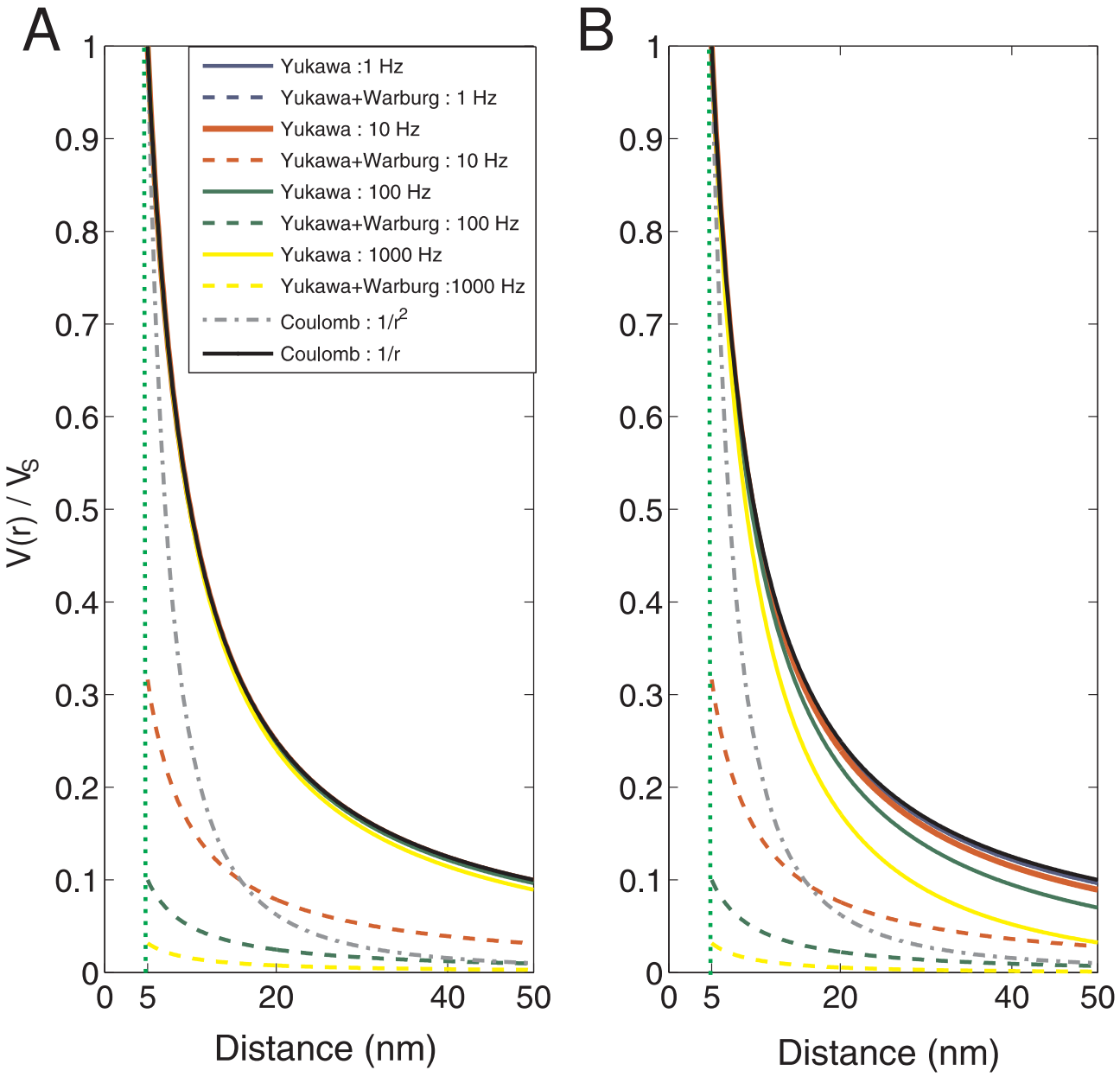

Figure 1

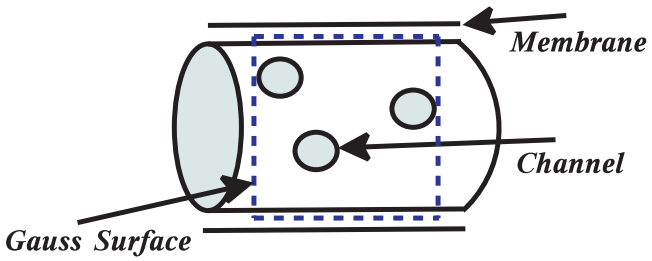

Figure 2

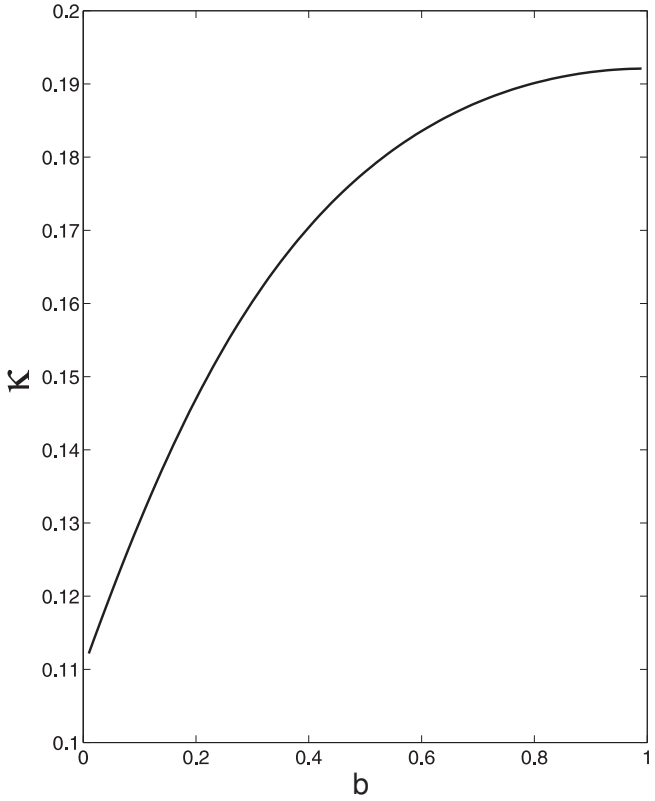

Figure 3